

## SHORT REPORT

# Acute sensory and autonomic neuropathy: possible association with Coxsackie B virus infection

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## Abstract

**This report describes a 26 year old woman with a Coxsackie B virus infection complicated by an acute pandysautonomic and sensory neuropathy. Electrophysiological studies suggested an axonal neuropathy. A sural nerve biopsy performed early in the disease showed axonal degeneration with a virtual absence of unmyelinated fibres and moderate loss of myelinated fibres, mainly affecting the small fibres; this differs from previous reports. An immune-mediated or direct virus action might explain the pathogenesis of this unusual evolution of a viral infection.**

## Case report

A 26 year old Venezuelan woman was examined for blackout spells (that occurred when changing from a recumbent to an upright position), blurred vision and photophobia, ageusia, dry mouth and eyes, nausea, constipation, urinary retention and overflow incontinence, and transient confusion. She was seven weeks pregnant and previously healthy. She was referred with fever and headache, in

association with diffuse mucosal and cutaneous maculopapular and vesicular erythema, for 10 days previously. The physical examination showed marked postural hypotension (supine blood pressure 120/80 mm Hg, unobtainable in a standing position) and fixed tachycardia ( $>100/\text{min}$ , unchanged with changes of position). There was a total absence of sweating, and hair and fingernails were dystrophic. Pupils were normal in size but unequal; the larger right pupil was unreactive to light, and accommodation, whereas the left pupil reacted slightly to light. Extraocular movements, pursuit and convergence were intact; corneal reflexes were present. Lacrimation was completely absent. The salivary flow was reduced and taste was distorted.

The other cranial nerves were unremarkable. Strength was mildly impaired in the distal limb muscles; moderate limb dysmetria was observed. Light touch sense was impaired over the neck, the upper trunk and the proximal part of the arms, especially on the right side. Pain sensation was markedly impaired or absent over the upper arms and the trunk, apart from a patchy area including dermatomes from D6 to D10. Thermal discrimin-

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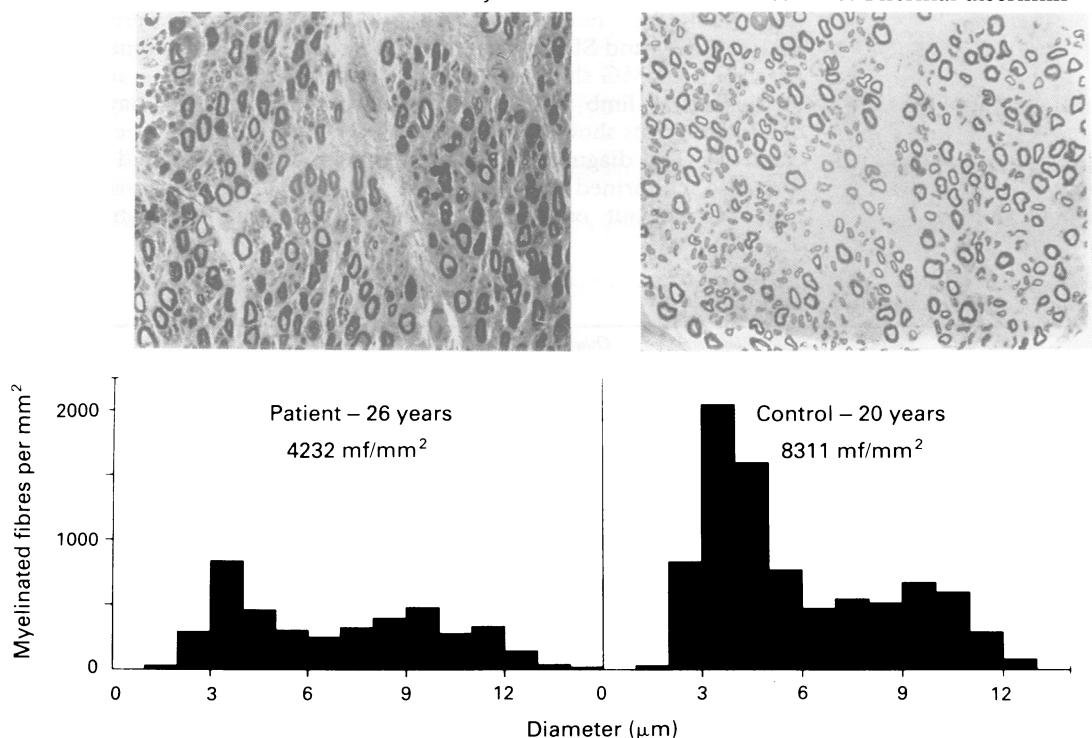


Figure Sural nerve biopsy: semithin sections (top) and myelinated fibre histograms (bottom) of the patient (left) and a normal control (right), showing myelinated fibre loss predominantly affecting small fibres (toluidine blue,  $\times 400$ ).

Table 1 Evolution of electrophysiological findings

	NV				Left median nerve				Right median nerve				NV				Left peroneal nerve			
Day	10	30	50	130	10	30	50	130	10	30	50	130	10	30	50	130	10	30	50	130
Distal latency (ms)	<4.5	2.4	3	2.8	2.7	2.3	4.9*	—	2.7	<5.5	2.6	3.6	5.6*	4.5						
Motor conduction velocity (m/s)	>49	50	50	52.4	48.8*	55	53.4	—	50.4	>43	48.5	42*	42.6*	39.4*						
MAP amplitude (mV)	>6	8	10	10	5.6*	12	10	—	6.1	>3	4.0	5	3*	1.1*						
Sensory conduction velocity (m/s)	>40	48.2	45	40.6	37.5*	52.5	35.2*	—	40.3											
SAP amplitude (µV)	>10	9*	2.5*	1.6*	1.4*	9*	2.4*	—	0.4*											
F wave:																				
Frequency (%)	>20	100	96	85	50	—	95	—	80	>5	30	85	80	65						
Min latency (ms)	<30	24	26	28.2	28	—	30*	—	28.6	<50.7	45	47.8	53*	51.8						
Mean latency (ms)	<32	27.9	26.9	29.1	29	—	31.4	—	30.1	<53	48.3	50	54.6*	53.1						
Max latency (ms)	<34	32	30	32.7	30.2	—	37*	—	33.3	<56.3	52	55	55.5*	54.9						

\*abnormal values

—not examined

NV normal values

ation was similarly but more diffusely impaired; hypoaesthesia was found in the proximal extremities and in the trunk, with the exception of the left middle thoracic dermatomes; cold sensation was lost in the distal part of the legs. Proprioception and vibration were present. The ankle reflexes were diminished and abdominal reflexes absent. Walking could not be examined. She required catheterisation because of difficulty in urinating and absent bladder distension sensation; the abdomen was distended and bowel sounds were absent, with radiological evidence of paralytic ileus.

A few days later she complained briefly of painful attacks in the extremities. The laboratory tests at the onset of the disease presented elevated plasma (1/1024; 1/1024 10 days later) and CSF (1/32; 1/128 10 days later) values of anti-Coxsackie B1, B2, B3 virus antibodies. CSF protein was slightly elevated (1120 mg/l); there were three mononuclear cells/ml. Antinuclear antibodies were present (1/640) and circulating immune complexes were slightly increased (2.1 µg/ml; normal value 1.5 < 1.5). Known causes of acquired dysautonomia were carefully excluded. Cerebral NMR was normal, as was the EEG, BAEPs, VEPs and SEPs (median and peroneal nerves); the EMG showed partial denervation in the distal limb muscles and the nerve conduction tests showed an axonal neuropathy (table 1). The diagnosis of pandysautonomia was also confirmed by autonomic function tests carried out on the tenth day: blood

pressure response to standing was 40 mm Hg (normal < 30); sustained handgrip 9 mm Hg (normal > 10); cold pressure test was 0 mm Hg (normal > 10); deep breathing (variation in beats/minute) was 3 (normal > 10); lying to standing could not be evaluated; Valsalva ratio was 1 (normal > 1.1); and sympathetic skin response was absent (methods and normal values of the cardiovascular reflex tests according to Ewing<sup>1</sup>). Five days after the onset of the neurological manifestations pregnancy was terminated. A sural nerve biopsy performed five days later revealed moderate loss of myelinated fibres (4232/mm<sup>2</sup>) especially of those of small diameter, which amounted to 51.3% (normal percentage of myelinated fibres of diameter < 7 µ: 55–68%,<sup>2</sup> and there was a complete absence of unmyelinated fibres (fig). Active axonal degeneration was present in the majority of teased fibres.

Approximately one month from the onset of the disease, slight tear and saliva production began and the patient's sense of taste returned. Decreased muscle strength (Medical Research Council Grade 4/5 diffusely) was noted. When the arms were extended fine tremor and hand dystonia were noticed. She had paresthesia and sensory impairment extending to the lower face and scalp, and to the distal part of the arms. Ten days later the patient complained of burning nocturnal pain in the extremities which lasted for three days, and abdominal colic. Orthostatic hypotension persisted but she was asymptomatic and could walk a few

Table 2 Reports of acute autonomic neuropathy

Author	Age (years)	Sex	Cholinergic/adrenergic	Other neurological deficit	CSF protein	Recovery time	Remarks
Appenzeller <i>et al</i> <sup>5</sup>	6	M	both	areflexia	normal	complete (16 years)	not acute
Colan <i>et al</i> <sup>6</sup>	9	F	both	severe sensory loss with ataxia and areflexia	1.30 g/l	autonomic good, sensory poor (18 months)	
Yahr <i>et al</i> <sup>7</sup>	13	F	both (partial)	decreased reflexes	1.20 g/l	good (6 months)	
Hopkins <i>et al</i> <sup>8</sup>	28	F	both	—	normal	complete (4 months)	mononucleosis infection
Okada <i>et al</i> <sup>9</sup>	37	M	both (partial)	decreased reflexes	normal	moderate (2 years)	
Okada <i>et al</i> <sup>9</sup>	43	M	both (partial)	—	normal	good (1 year)	
Goulon <i>et al</i> <sup>10</sup>	40	M	both (partial)	ophthalmoplegia, ataxia, left Babinski sign	normal	good (3 months)	
Wichser <i>et al</i> <sup>11</sup>	47	F	both (partial)	urinary incontinence, urgency	1.02 g/l	partial (14 months)	amyloidosis?
Young <i>et al</i> <sup>3,4</sup>	49	M	both (partial)	—	1.28 g/l	complete (17 months)	
Fagius <i>et al</i> <sup>12</sup>	31	M	both	severe sensory loss with ataxia and areflexia	0.96 g/l	poor (45 months)	
Low <i>et al</i> <sup>13</sup>	46	F	both	mild sensory loss (thermal)	normal	partial (5 years)	
Low <i>et al</i> <sup>13</sup>	74	F	both (partial)	—	0.91 g/l	Not known	
Taubner <i>et al</i> <sup>14</sup>	62	F	both (partial)	severe sensory-motor deficit	0.44 g/l (IgG)	poor (4 months)	
Neville <i>et al</i> <sup>15</sup>	13	F	both (partial)	mild sensory-motor deficit (demyelinating neuropathy)	normal (IgG)	Not known	herpes simplex virus infection
Feldman <i>et al</i> <sup>16</sup>	30	F	both (partial)	—	0.70 g/l	Not known	axonal neuropathy
Present case	26	F	both	mild sensory-motor deficit (severe 2 months later)	1.12 g/l	autonomic partial, somatic poor (12 months)	Coxsackie B virus infection

Right peroneal nerve				NV	Left sural nerve				Right sural nerve			
10	30	50	130		10	30	50	130	10	30	50	130
2.9	5.3	4.5	4.2									
49.2	38.3*	38.1*	37.8*									
3*	2.3*	1.6*	1.5*									
				>38	48	—	—	—	46	biopsy		
				<11	10*	—	absent*	—	14	biopsy		
—	80	90	85									
—	50.6	53.3*	50.6									
—	55.7*	55.2*	52.8									
—	58.4*	59.9*	56.5*									

steps. Impairment of pain sensation and thermal discrimination were more advanced, with the only exception of the face, palms and the soles of the feet. Vibration sense was moderately reduced in the lower limbs.

Fifty days from the onset of the disease, the patient had repeated blackout spells while sitting, and she complained of general deterioration with asthenia and numbness of the left side of the face and chest. Loss of light touch sensation was detected in cranial, cervical and brachial dermatomes, and over the upper chest on the left side. Ten days later she was able to empty her bladder and gastrointestinal peristalsis was normal. Sweating appeared over the forehead and axillae. She complained of disturbing numbness of the extremities with marked subjective sensation of rigidity and of patchy and migrating pains from different parts of the body; sensory examination was unchanged. Walking was still difficult because of a severe sensory ataxia. A month later she experienced occasional hypertension in the recumbent position.

One year after the onset of the disease the neurological examination showed no motor deficit; marked sensory ataxia; persistent tactile, pain and thermic deficit; occasional blurred near vision; partial recovery of salivation and lacrimation; patchy sweating on the back and armpits; subclinical postural hypotension; and persistent constipation with normal sphincter control.

## Discussion

Acute pandysautonomia is a rare syndrome characterised by severe sympathetic and parasympathetic postganglionic impairment with relative or complete sparing of motor and

sensory function. It was described as a clinical entity by Young *et al.*<sup>3,4</sup> Other studies followed (table 2), but the pathological basis and the aetiology still remain unclear. Electrophysiological and morphological studies were carried out in only a few cases in the early phase of the disease and these reports differ in their conclusions. In our case, the pathological basis was an axonal degeneration, which was proven by the sural nerve biopsy. Our findings do not confirm whether the peripheral nerves are directly damaged, or the primary lesion lies in the autonomic and dorsal root ganglia, as previously reported.<sup>12</sup> A viral cause for the disease has been proposed (table 2). In our case pandysautonomia and sensory neuropathy were associated with evidence of a Coxsackie B virus infection, and high and rising levels of anti-Coxsackie B virus antibodies. This infection could be the possible origin of the pandysautonomic neuropathy, perhaps by direct viral damage or by eliciting an abnormal immune response.

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